



**PERINATAL AND CHILDHOOD
HEPATITIS.....
WHAT ABOUT THE CHILDREN?**

John T. Stutts, MD, MPH

University of Louisville School of Medicine
Department of Pediatrics

Division of Pediatric Gastroenterology, Hepatology and Nutrition



HEPATITIS A

- Single-stranded RNA hepatitis A virus (HAV)
- Mode of transmission
 - Fecal-oral (foodborne or waterborne)
 - There is no carrier state or chronic infection
- Incubation period
 - 15-40 days (mean 28)



HEPATITIS A

- Clinical features:
 - Often asymptomatic (especially under 6 years of age).
 - Only 30% of infants and preschool-aged children exhibit symptoms.
 - HAV is acute and self-limited.
 - Associated symptoms +/-:
 - anorexia • emesis • fevers • jaundice
 - malaise • diarrhea • headache

HEPATITIS A

- Clinical features (continued):
 - Characterized by clinical improvement with the onset of jaundice.
 - Normalization of bilirubin and transaminases within 4-6 weeks.
 - Acute liver failure is possible – but very rare.



HEPATITIS A

- Diagnosis
 - Confirmed by the presence of anti-HAV IgM antibody in serum.
 - Laboratories:
 - Liver panel
 - PT/INR
 - HAV-IgM



HEPATITIS A

- Prevention
 - HAV vaccine
 - Universally recommended for all children between 12-24 mo. of age.
 - Catch-up immunization for older, unimmunized children.
 - Offer HAV vaccine to HAV-exposed family members or close contacts.



HEPATITIS A

- Prevention
 - HAV immune globulin indications
 - Travel to endemic areas.
 - Post exposure prophylaxis within 14 days after exposure to food handled by someone with HAV, or persons exposed to a family member with HAV.



HEPATITIS B

- Double-stranded DNA hepatitis B virus (HBV)
- Mode of transmission
 - Vertical (perinatal transmission)
 - Parenteral
 - Sexual
- Incubation period 50-180 days



HEPATITIS B

- Perinatal transmission
 - Rates vary from 20-90%
 - Depends on maternal HBsAg titer and HBeAg status



HEPATITIS B

- Carrier state and chronic infection state
 - A carrier state is a persistent infection with presence of HBsAg, but without biochemical or clinical signs of ongoing hepatic injury.
 - HBV carriers are infectious.



HEPATITIS B

- At-risk populations
 - Infants born to HBV-infected women
 - Infants/children living in community groups with endemic HBV
 - Immigrants/adopted children from regions of the world with high prevalence of HBV
 - Household contacts of individuals with chronic HBV
 - Adolescents engaging in high-risk behaviors



HEPATITIS B

- Development of chronic disease varies based on the age of acquisition
 - Infants: 90% chance of developing chronic disease
 - Children 1-5 years: 30% chance
 - Children > 5 years: 6% chance



HEPATITIS B

- Clinical features
 - Perinatal HBV acquisition is usually asymptomatic; however, if mother is HBeAg positive at birth, ~ 6% of infants will develop acute liver failure by 2-3 months of age.

HEPATITIS B

- Clinical features (continued)
 - Chronic active hepatitis
 - Persistence of HBsAg > 6 months and elevated ALT and AST levels.
 - Of the neonates who become chronic carriers, many develop an immune tolerant phase = normal ALT/AST despite high HBV DNA levels and persistent HBsAg and HBeAg positivity (and negative antibodies).
-



HEPATITIS B

- Diagnosis
 - Confirmed by detection of HB surface antigen (HBsAg) on two separate testings at least 6 months apart.
 - Laboratories: Liver panel, HBV: sAg, sAb, eAg, eAb
 - Positive HBsAg = active infection
 - Positive HBeAg = high infectivity
 - HBeAg negative & HBeAb positive = seroconversion with clearance of actively replicating virus
 - Positive HBsAb is rare = protective immunity
-



HEPATITIS B

- Annual rate of spontaneous clearance (conversion to HBeAg negative and HBeAb positive)
 - 0-3 years of age < 2%
 - > 3 years of age ~ 5%
- Check HBV DNA (viral load) if considering treatment.
- Check liver histology (biopsy) if considering treatment.



HEPATITIS B

- Treatment
 - Subcutaneous weekly pegylated interferon-alpha injections for 24 weeks.
 - Response = nondetectable HBV DNA and seroconversion to HBeAb positive (HBeAg negative).
 - However pegylated interferon therapy approved for ≥ 3 years of age only.
 - Seroconversion rates: ~30%.



HEPATITIS B

- Prevention
 - HBV vaccine:
 - Universally recommended for all infants (series of 3 doses over 6-9 months).
 - Catch up immunizations for older, unimmunized children.
 - HBV-exposed family members/close contacts.



HEPATITIS B

- Prevention (continued)
 - HBV immune globulin indications for use:
 - Infants born to HBsAg positive mothers.
 - Postexposure prophylaxis within 24 hours after exposure (if no vaccination in the past)
 - Household contacts
 - Avoid sharing of shavers, toothbrushes, nail clippers, tweezers



HEPATITIS B

- Prevention (continued)
 - Universal precautions for handling abrasions, bleeding, etc.
 - Screening for hepatocellular carcinoma (HCC): increased risk in the setting of chronic HBV hepatitis.
 - Screening modalities: annual alpha fetoprotein, liver ultrasound.



HEPATITIS C

- Single-stranded RNA hepatitis C virus (HCV).
- Mode of transmission
 - Vertical (perinatal transmission)
 - Parenteral
 - Sexual
- Incubation period: 30-150 days



HEPATITIS C

- Perinatal transmission
 - Rates are ~ 5%.
 - Rates increase to 15-20% if the mother is coinfectd with HIV.



HEPATITIS C

- Clinical features
 - Chronic infections will develop in 60-80% of exposed children.
 - Majority of patients are asymptomatic in childhood.

HEPATITIS C

- Clinical features (continued)
 - Acute liver failure from HCV infection in immunocompetent patients has not been reported.
 - End-stage liver disease with cirrhosis in childhood – reported but rare.



HEPATITIS C

- Diagnosis
 - Laboratories: liver panel, HCV IgG Antibody (after 18 mos. of age) and HCV RNA (after 2 mos. of age)
 - Positive anti-HCV antibody (IgG) after > 18 months of age = exposure to HCV.
 - Active infections can only be confirmed by positive HCV RNA.



HEPATITIS C

- Diagnosis (continued)
 - HCV genotype analysis indicated if treatment is being considered.
 - HCV RNA testing in the first 2 months of life is problematic:
 - false positives (due to transient viremia)
 - false negatives (due to low levels not detectable)
 - So.... wait until after 2 months of age to check HCV RNA and repeat test 6 months later.
 - Spontaneous clearance after perinatal acquisition – 20-45%.
-



HEPATITIS C

- Treatment
 - Subcutaneous weekly pegylated interferon-alpha injections for 48 weeks (genotypes 1 or 4) or 24 weeks (genotypes 2 or 3) plus ribavirin.
 - Response = nondetectable HCV RNA by the end of the treatment period.
 - Pegylated interferon/ribavirin therapy approved for ≥ 3 years of age.
 - Seroconversion – overall 59% (genotypes 2/3 have higher rates of conversion than genotype 1)



HEPATITIS C

- Prevention
 - HCV vaccine: none available
 - HCV immune globulin: none available
 - Household contacts: avoid sharing of shavers, toothbrushes, nail clippers, tweezers



HEPATITIS C

- Prevention (continued)
 - Universal precautions for handling abrasions, bleeding, etc.
 - Screening for hepatocellular carcinoma (HCC): increased risk in the setting of chronic HCV hepatitis.
 - Screening modalities: annual alpha fetoprotein, liver ultrasound.



HEPATITIS D

- Defective RNA hepatitis D virus
- Mode of transmission
 - Vertical (perinatal transmission)
 - Parenteral
 - Sexual
- Incubation phase: 20-90 days



HEPATITIS D

- Clinical features
 - Coinfection with hepatitis D is more severe than hepatitis B alone.
 - Can progress more rapidly to liver cirrhosis and failure.



HEPATITIS D

- Diagnosis
 - Confirmed by the presence of anti-HDV antibody.
- Prevention
 - HDV vaccine: none available
 - HDV immune globulin: none available



HEPATITIS E

- Singled stranded RNA hepatitis E virus (HEV)
- Mode of transmission
 - Fecal-oral (foodborne, waterborne)
 - Reports of contaminated blood products
 - There is no carrier state or chronic infection.
- Incubation period: 15-40 days



HEPATITIS E

- Clinical features
 - Acute, self-limited
 - Associated symptoms +/-:
 - anorexia
 - malaise
 - fevers
 - headache
 - emesis
 - diarrhea
 - jaundice
 - Infection can be severe in pregnant women (3rd trimester), with 20% mortality.



HEPATITIS E

- Diagnosis
 - Confirmed by presence of anti-HEV IgM antibody in serum.
 - Laboratories
 - Liver panel
 - PT/INR
 - HEV-IgM



HEPATITIS E

- Prevention
 - No HEV vaccine is available.



WHAT ABOUT BREASTFEEDING?

- Breastfeeding is not contraindicated as it does not increase the risk of transmission of HBV or HCV.
- Although HBV DNA has been detected in the colostrum of HBsAg positive mothers, a study of 147 infants revealed no relationship between breastfeeding and subsequent HBV infection.



WHAT ABOUT BREASTFEEDING?

- An additional study of 369 breastfeeding neonates showed no transmission in any infant.
- However, mothers who are breastfeeding should exercise care to prevent bleeding from cracked nipples.



WHAT ABOUT CESAREAN DELIVERY?

Is it necessary?

- Well-conducted controlled trials have been unable to show prevention of maternal-infant transmission.
- Therefore, cesarean delivery is not routinely recommended for carrier mothers.



WHAT ABOUT ADOPTION?

- Family members (adult and children) of internationally adopted children are recommended to receive Hepatitis B vaccination before the child's arrival.
- To allow adequate time for response, the first dose of hepatitis B vaccine should be administered 4-6 months before the child joins the family, if possible.



SUMMARY & RECOMMENDATIONS

- Hepatitis A
 - Risk of perinatal and neonatal transmission is small.
 - Neonatal HAV is primarily due to contamination of food, water and blood products.
 - Most neonates with HAV are asymptomatic.
 - Treatment is supportive care.



SUMMARY & RECOMMENDATIONS

- Hepatitis B
 - Vertical transmission can occur near the time of delivery.
 - Neonates rarely show clinical or biochemical signs of disease at birth.
 - Serologic testing is necessary to make the diagnosis.
 - No therapy is available for acute infection.



SUMMARY & RECOMMENDATIONS

- Hepatitis B (continued)
 - Prevention of perinatal transmission by immunization reduces vertical transmission rates.
 - Infants, including preterm infants, born to women with positive serology should be given HBIG along with HBV vaccine.
 - Infants born to women who are HBsAg negative should receive hepatitis B vaccine as part of routine childhood immunizations.



SUMMARY & RECOMMENDATIONS

- Hepatitis C

- Vertical transmission can occur and is higher in the mother coinfecting with HIV.
- Overall, the transmission rates in the neonatal period are low.
- Breastfeeding does not appear to increase transmission (defer if cracked/bleeding nipples).



SUMMARY & RECOMMENDATIONS

- Hepatitis C (continued)
 - Newborns with HCV infection are normally asymptomatic.
 - Liver disease remains mild throughout childhood.
 - No preventions have been identified to preclude perinatal transmission.
 - Combined therapy of ribavirin and pegylated interferon-alpha – 40-90%.
-



SUMMARY & RECOMMENDATIONS

- Hepatitis D
 - Vertical transmission is rare.
 - Only transmitted as a coinfection with HBV.
 - Preventive measures for HBV infection are also protective against HDV.



SUMMARY & RECOMMENDATIONS

- Hepatitis E
 - Rare in the United States.
 - Endemic in many developing countries.
 - Vertical transmission has been observed.
 - There is no specific therapy for infants of mothers with HEV infection.



SUMMARY & RECOMMENDATIONS

PREVENTION IS THE KEY!!!





Thank You!



THE HEPATITIS VIRUSES: CHARACTERISTICS AND TERMINOLOGY OF ASSOCIATED ANTIGENS AND ANTIBODIES

MARKER	DEFINITION	SIGNIFICANCE OF MARKER
Serologic Markers of HAV		
Anti-HAV IgM	Antibody (IgM) directed against HAV	Current or recent infection
Anti-HAV IgG	Antibody (IgG) directed against HAV	Previous infection/vaccine and protective immunity
Serologic Markers of HBV		
HBsAg	Hepatitis B surface antigen; found on surface of intact virus and in serum as free particles	Active HBV infection
HBcAg	Hepatitis B core antigen, found within virus core	Detectable in liver tissue
HBeAg	Hepatitis B e antigen; soluble antigen produced during self-cleavage of HBcAg	High infectivity
HBV DNA	DNA of HBV (PCR test)	Active HBV replication
Anti-HBs IgG	Antibody (IgG) to HBsAg	Protective immunity
Anti-HBc IgM	Antibody (IgM) to HBcAg	Early infection
Anti-HBc IgG	Antibody (IgG) to HBcAg	Indicates infection
Anti-HBe	Antibody to HBeAg	Resolution of active viral replication



THE HEPATITIS VIRUSES: CHARACTERISTICS AND TERMINOLOGY OF ASSOCIATED ANTIGENS AND ANTIBODIES

MARKER	DEFINITION	SIGNIFICANCE OF MARKER
Serologic Markers of HCV		
Anti-HCV	Antibody (IgG) to HCV	Exposure to HCV. Not protective
HCV RNA	RNA of HCV (PCR test)	Active HCV infection
Serologic Markers of HDV		
HDVAg	Hepatitis D antigen	HDV infection
Anti-HDV	Antibody (IgM/IgG subclass) to HDV	Exposure to HDV
HDV RNA	RNA of HDV (PCR test)	Active HDV replication
Serologic Markers of HEV		
HEVAg	Antigen associated with HEV	Stool test; recent infection
HEV RNA	RNA of HEV (PCR test)	Early HEV infection
Anti-HEV	Antibody (IgM) to HEV	Early HEV infections
Anti-HEV	Antibody (IgG) to HEV	Protective immunity

Adapted from the NASPGHAN Fellows Concise Review of Pediatric Gastroenterology, Hepatology and Nutrition



REFERENCES

1. The NASPGHAN Fellows Review
 2. O'Donovan DJ. Hepatitis viruses and the newborn: Clinical manifestations and treatment. UpToDate 2014.
 3. Lee H, Lok AS. Hepatitis B and Pregnancy. UpToDate 2014.
 4. Staat MA. International Adoption: Immunization considerations. UpToDate 2014.
 5. El-Shabrawi MH, Kamal NM. Burden of pediatric hepatitis C. *World J Gastroenterol*. 2013 Nov 28;19(44):7880 – 8.
 6. Hsu EH, Murray KF. Hepatitis B and C in children. *Nat Clin Pract Gastroenterol Hepatol*. 2008;5:311-320.
 7. Jonas MM, Block JM, Haber BA, et al; for the Hepatitis B Foundation. Treatment of children with chronic Hepatitis B virus infection in the United States: patient selection and therapeutic options. *Hepatology* 2010;52(6):2192-205.
 8. Narkewicz MR, Cabrera R, Gonzalez-Peralta RP. The “C” of viral hepatitis in children. *Semin Liver Dis*. 2007;3:295-311.
 9. Schwarz KB, Gonzales-Peralta RP, Murray KF, et al; for the Peds-C Clinical Research Network. The combination of ribavirin and peginterferon is superior to peginterferon and placebo for children and adolescents with chronic hepatitis C. *Gastroenterology*. 2011;140(2):450-458.
 10. Suchy FJ, Sokol RJ, Balistreri WF, eds. *Liver Diseases in Children: 3rd ed.* New York NY. Cambridge University Press; 2007.
 11. HAV, hepatitis A virus; HBV, hepatitis B virus, HBcAg, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus, PCR, polymerase chain reaction.
 12. Modified from Hochman JA, Balistreri WF. Acute and chronic viral hepatitis. In: Suchy FJ, Sokol RJ, Balistreri WF, eds. *Liver Disease in Children*. New York, NY. Cambridge University Press 2007: 370.
-